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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/655,540	CARTER ET AL.	
	Examiner	Art Unit	
	RUSSELL S. NEGIN	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 February 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Comments

Applicants' amendments and request for reconsideration in the communication filed on 27 November 2007 are acknowledged and the amendments are entered.

Claims 1-26 and 30-31 are pending and examined in this Office action.

Claim Objections

The objection to claim 1 because of informalities is withdrawn in view of amendments to the claim on 27 November 2007.

Drawings

The amended drawings filed on 2/2/04 are objected to because they do not properly indicate that they are "Replacement" or "New" sheets. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement

sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either “Replacement Sheet” or “New Sheet” pursuant to 37 CFR 1.121(d). It is noted that the requirement to label amended drawings as "Replacement Sheets" was set forth in 68 Federal Register 38611, published 6/30/03. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The rejections of claims 1-13, 17-18, 21-22, 25 and 30-31 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn in view of amendments to the set of claims filed on 27 November 2007.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following rejection is newly applied:

Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 recites the phrase on lines 7-8 stating, "algebraic manipulations relating full and reduced ray mixture models," where it is unclear as to how the mixture models are to be related.

Claim Rejections - 35 USC § 102

The following rejection is reiterated:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 14 is rejected under 35 U.S.C. 102(b) as being anticipated by Gennings et al. [Journal of Agricultural, Biological, and Environmental Statistics, volume 2, 1997, pages 198-211].

Claim 14 is drawn to a method of determining an interaction threshold between agents in a group or mixture comprising generating a model that permits estimation of the boundaries between a region of additivity and a region of interaction of said agents wherein said generation is carried out in order to detect, characterize or predict an outcome caused by exposure to said agents in said group or mixture.

The article of Gennings et al. (1997), entitled, "Detection of departures from additivity in mixtures of many chemicals with a threshold model," states on the last seven lines of page 199:

> Suppose that we are interested in studying the interaction among c chemicals in combination, where dose-response information is available on each single chemical. Assume that the existence of a threshold is reasonable for these chemicals. Further, suppose that we are particularly interested in the effect associated with certain combinations of these chemicals. We propose to construct a threshold additivity model that can be used to predict a response at each combination of interest. The observed response at these combination points can then be compared to that predicted under the assumption of additivity.

Consequently, Gennings et al. (1997) teaches a threshold additivity model for the purpose of analyzing groups or mixtures.

Such a threshold additivity model is displayed quantitatively as equation 1.1 on page 201 of Gennings et al. (1997). The top "branch" of equation 1.1 indicates an additivity model. Above a certain threshold, δ, the generation of a region containing a departure from additivity from the elements of the group (i.e. a region of interaction) is witnessed. The results are plotted in Figures such as Figure 1 of Gennings et al. (1997).

Response to Arguments:

Applicant's arguments filed 27 November 2007 have been fully considered but they are not persuasive.

Applicant first alleges on pages 11-12 of the Remarks that there is confusion on the Examiner's part on the difference in meanings between "interaction threshold model" and "threshold additivity model." The examiner maintains, contrary to the arguments, that the "threshold additivity" taught by Gennings et al. (1997) is the same as the claimed "interaction threshold" for the following reasons:

Applicant argues on page 11 of the Remarks that an interaction threshold is the threshold boundary at which the additive response combining elements into a mixture

ends. In other words, above the interaction threshold boundary, the additive properties of the mixture no longer exist. Applicant even redefines interaction as "non-additivity" on line 6 of page 12 of the Remarks. However, on page 201 of Gennings et al. (1997), equation 1.1 illustrates a boundary (δ) between a mixture with additive properties and a mixture with non-additive properties (i.e. “interactions”). While applicant argues on page 12 of the Remarks that this additivity is an assumption, Figure 1 on page 200 of Gennings et al. (1997) plots data illustrating this model showing additive and non-additive regions. Consequently, the definition in the prior art of “threshold additivity model" encompasses the definition of "interaction [non-additivity] threshold model" provided by applicants in the Remarks.

In response to applicant's argument that the references fail to show certain features of applicant’s invention, it is noted that the features upon which applicant relies (i.e., the existence of “regions” and not just points and the availability of single chemical data are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant next argues on page 14 of the Remarks that Figure 1 of Gennings et al. (1997) is a hypothetical model used to demonstrate additive data only. This is not persuasive because there is no information in Gennings et al. (1997) stating that Figure 1 of Gennings et al. (1997) is hypothetical. In addition, even assuming that this figure is hypothetical, one of skill in the art would have been able to make and/or use the

model/plot in view of the equations on page 201 and the data in the Example on pages 206-210, which teaches how to construct such a three dimensional plot.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following rejections are reiterated:

Claims 1-13 and 15-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gennings et al. [Journal of Agricultural, Biological, and Environmental Statistics, volume 3, pages 1-16, 1998] as applied to claim 14 above in further view of Gennings et al. [Journal of Agricultural, Biological, and Environmental Statistics, volume

2, 1997, pages 198-211]. The first reference is referred to in this Office action as Gennings et al. (1998); the second reference is referred to in this Office action as Gennings et al. (1997).

General discussion of claims 1, 6, 15, 17, 19, and 21

Claim 1 is drawn to a method of detecting interactions among agents in a group or mixture comprising seven steps.

The preamble of claim 1 indicates a method of detecting an interaction among agents in a group or mixture using fixed-ratio ray design and determining whether subsets of said agents also interact. The first step (step a) of instant claim 1 recites determining an additivity model from single dose-response data. The second step (step b) of instant claim 1 recites fitting a mixture model in terms of total dose to mixture-dose response data from fixed-ratio rays for said agents in said group or mixture. The third step (step c) of instant claim 1 recites comparing the additivity and mixture models. The fourth and fifth steps (steps d and e) of instant claim 1 recite removing a subset of agents from the group or mixture and repeating this step for multiple subsets, respectively. The sixth step (step f) of instant claim 1 recites determining the interaction of agents by utilizing the statistical methods based on the results of the fourth and fifth steps of the method. The seventh step (step g) of claim 1 provides the results in the form of a plot or table.

Claim 6 is drawn to a method of detecting interactions among agents in a group or mixture comprising six steps.

The preamble of claim 6 indicates a method of detecting an interaction among agents in a group or mixture using fixed-ratio ray design and determining whether subsets of said agents also interact. The first step (step a) of instant claim 6 recites fitting a polynomial additivity to dose-response data. The second step (step b) of instant claim 6 is statistical analysis of higher order terms in the polynomial model. The third and fourth steps (steps c and d) of instant claim 6 recite removing a subset of agents from the group or mixture and repeating this step for multiple subsets, respectively. The fifth step (step e) of instant claim 6 recites determining the interaction of agents by utilizing the statistical methods based on the results of the third and fourth steps of the method. The sixth step (step f) of claim 6 provides the results in the form of a plot or table.

Claim 14 is described in the rejection above.

Claims 15 and 17 further limit claim 14 described above further incorporating limitations similar to those of instant claim 1.

Claims 19 and 21 further limit claim 14 described above further incorporating limitations similar to those of instant claim 6.

The study of Gennings et al. (1998), entitled, "Combination threshold models with design optimization along fixed-ratio rays," states in the abstract:

> Threshold models are useful in concentration-effect studies to describe regions of exposure that result in background response. These models are parameterized to estimate the background response, the concentration-effect relationship, and the join-point between the two, called the threshold. If the threshold is different than zero, then it can be inferred that exposure to the chemical at regions below the threshold do not increase risk above background. When the exposure is to many chemicals, fixed-ratio ray designs can be used to assess risk to single chemicals and to specified mixtures of chemicals. This article describes the inference resulting from use of a threshold model for correlated binary data supported by a ray design. An example of the effect of three hepatotoxins in the development of rats is provided. In addition, a two-stage

simultaneous optimal design criterion is described for the threshold model along rays of fixed ratios. The approach is illustrated through a simulation study of the hepatotoxin data.

Consequently, Gennings et al. (1998) teaches usage of mixtures and analysis (using fixed ratio rays) of mixture data in rats (test subjects).

The first step (step a) of instant claim 1 recites determining an additivity model from single dose-response data. Gennings et al. (1998) teaches the use of an additivity model in section 2.2 on page 4, entitled, "Estimation of an additivity threshold surface." The first equation in section 2.2 of Gennings et al. (1998) teaches such an additivity model quantitatively.

The second step (step b) of instant claim 1 recites fitting a mixture model in terms of total dose to mixture-dose response data from fixed-ratio rays for said agents in said group or mixture. The third step (step c) of instant claim 1 recites comparing the additivity and mixture models. A threshold mixture model is taught through section 2 on page 3 of Gennings et al. (1998), entitled, "Threshold model for proportional data," and section 2.1 on pages 3-4 of Gennings et al. (1998), entitled, "Simultaneous estimation along each ray using a threshold model." Section 2.3.2 on pages 5-6 of Gennings et al. (1998), entitled, "Comparison of predicted thresholds along each mixture ray to the location of the threshold under additivity," compares the additive and mixture models by using thresholds.

The fourth and fifth steps (steps d and e) of instant claim 1 recite removing a subset of agents from the group or mixture and repeating this step for multiple subsets, respectively. The sixth step of instant claim 1 recites determining the interaction of

agents by utilizing the statistical methods based on the results of the fourth and fifth steps of the method. In the example study in section 4 of Gennings et al. (1998) on pages 8-12 of Gennings et al. (1998), Table 4 of Gennings et al. (1998) on page 11 illustrates modeling the interaction of three agents (DEHP, HEPT, and TCE) by removing two of the three agents, and then examining the effects of a mixture on the mixture in Ray 4, which is a 70:1:29 mixture of DEHP, HEPT, and TCE, respectively. Table 3-5 on page 11-12 of Gennings et al. (1998) tabulate a plurality of full-ray groups. Figure 2 on page 10 if Gennings et al. (1998) is interpreted as a statistical hypothesis comparison between an additivity model and a mixture model (steps f and g).

However, Gennings et al. (1998) fails to teach that when the subsets of two agents are removed, the remaining agents (plural) must maintain their relative ratios (i.e. fourth step –step d of instant claim 1).

Gennings et al. (1997) teaches such a phenomenon in their study, entitled "Detection of departures from additivity in mixtures of many chemicals with a threshold model." Specifically, in comparing the plots Figures 1a and 1b on page 200 of Gennings et al. (1997), a subset of chemicals are removed and a subset of chemical remain. As is stated in the Figure caption:

> Figure 1. Three-dimensional representation of a threshold additivity surface between four chemicals over dose ranges of Chemical 1 and Chemical 2 when: (a) Chemical 3 and Chemical 4 are not included in the mixture (= 0) and (b) Chemical 3 = 0.1 and Chemical 4 = 0.1.

Consequently, while in Figure 1B, all of the constituents are in the mixture, in Figure 1A of Gennings et al. (1997), the subset of chemicals 3 and 4 are removed, leaving chemicals 1 and 2.

The purpose of the study of Gennings et al. (1997) is stated in the introduction, which states, "The evaluation of risk associated with mixtures of chemicals is often needed when the number of chemicals in the mixture is large when the concentration of individual chemicals is low."

With regard to claim 6, the first step (step a) of instant claim 6 recites fitting a polynomial additivity to dose-response data. Gennings et al. (1998) teaches the use of an additivity model in section 2.2 on page 4, entitled, "Estimation of an additivity threshold surface." The first equation in section 2.2 of Gennings et al. (1998) teaches such an additivity model quantitatively. Furthermore, the equation on page 1 of Gennings et al. (1998) illustrates such a polynomial to be used to determine additivity in dose response data. As there are three agents interacting in this specific case of Gennings et al. (1998), the highest order term that is not zero is a cubic term, indicating three components (i.e. second step- step b of instant claim 6).

The third and fourth steps (steps c and d) of instant claim 6 recite removing a subset of agents from the group or mixture and repeating this step for multiple subsets, respectively. The fifth step (step e) of instant claim 6 recites determining the interaction of agents by utilizing the statistical methods based on the results of the third and fourth steps of the method. In the example study in section 4 of Gennings et al. (1998) on pages 8-12 of Gennings et al. (1998), Table 4 of Gennings et al. (1998) on page 11 illustrates modeling the interaction of three agents (DEHP, HEPT, and TCE) by removing two of the three agents, and then examining the effects of a mixture on the

mixture in Ray 4, which is a 70:1:29 mixture of DEHP, HEPT, and TCE, respectively. Table 3-5 on page 11-12 of Gennings et al. (1998) tabulate a plurality of full-ray groups. Figure 2 on page 10 if Gennings et al. (1998) is interpreted as a comparison between an additivity model and a mixture model (steps f and g).

However, Gennings et al. (1998) fails to teach that when the subsets of two agents are removed, the remaining agents (plural) must maintain their relative ratios (i.e. third step of instant claim 6).

Gennings et al. (1997) teaches such a phenomenon in their study, entitled "Detection of departures from additivity in mixtures of many chemicals with a threshold model." Specifically, in comparing the plots Figures 1a and 1b on page 200 of Gennings et al. (1997), a subset of chemicals are removed and a subset of chemical remain. As is stated in the Figure caption:

> Figure 1. Three-dimensional representation of a threshold additivity surface between four chemicals over dose ranges of Chemical 1 and Chemical 2 when: (a) Chemical 3 and Chemical 4 are not included in the mixture (= 0) and (b) Chemical 3 = 0.1 and Chemical 4 = 0.1.

Consequently, while in Figure 1B, all of the constituents are in the mixture, in Figure 1A of Gennings et al. (1997), the subset of chemicals 3 and 4 are removed, leaving chemicals 1 and 2.

Claim 2 is dependent from claim 1 with the additional limitation of specifying a plurality of full ray groups. Table 4 of page 11 of Gennings et al. (1998) lists a plurality of full-ray groups.

Claim 3 is dependent from claim 1 with the additional limitation of carrying out the second and third steps of instant claim 1 for the subset of agents. Gennings et al. (1997) carries out such a process in Figure 1. Specifically, in comparing the plots Figures 1a and 1b on page 200 of Gennings et al. (1997), a subset of chemicals are removed and a subset of chemical remain. As is stated in the Figure caption:

> Figure 1. Three-dimensional representation of a threshold additivity surface between four chemicals over dose ranges of Chemical 1 and Chemical 2 when: (a) Chemical 3 and Chemical 4 are not included in the mixture (= 0) and (b) Chemical 3 = 0.1 and Chemical 4 = 0.1.

Consequently, while in Figure 1B, all of the constituents are in the mixture, in Figure 1A of Gennings et al. (1997), the subset of chemicals 3 and 4 are removed, leaving chemicals 1 and 2.

Claim 4 is dependent from claim 1 with the extra limitation of showing an additivity curve compared with a mixture curve. Figure 2 of Gennings (1998) on page 10 illustrates a comparison of additivity (i.e. model predicted) and mixture model (i.e. observed) with the purpose of comparing the two types of statistical analyses.

Claim 5 is dependent from claim 1 with the additional limitation of determining simultaneous confidence bands on the difference between the additivity curve and the mixture curve.

Confidence bands are described in the full paragraph of page 10 of Gennings et al. (1998), which states:

> As evidenced by the data points in Figure 2 and the p values in Table 3, the proportion of prenatal loss across litters is large. The 95% confidence interval for the threshold for DEHP covers the entire experimental region …[and] the threshold interval for total dose along the mixture ray.

The study of Gennings et al. (1998), entitled, "Combination threshold models with design optimization along fixed-ratio rays," states in the abstract:

> Threshold models are useful in concentration-effect studies to describe regions of exposure that result in background response. These models are parameterized to estimate the background response, the concentration-effect relationship, and the join-point between the two, called the threshold. If the threshold is different than zero, then it can be inferred that exposure to the chemical at regions below the threshold do not increase risk above background. When the exposure is to many chemicals, fixed-ratio ray designs can be used to assess risk to single chemicals and to specified mixtures of chemicals. This article describes the inference resulting from use of a threshold model for correlated binary data supported by a ray design. An example of the effect of three hepatotoxins in the development of rats is provided. In addition, a two-stage simultaneous optimal design criterion is described for the threshold model along rays of fixed ratios. The approach is illustrated through a simulation study of the hepatotoxin data.

Consequently, Gennings et al. (1998) teaches usage of mixtures and analysis (using fixed ratio rays) of mixture data in rats (test subjects).

Claim 7 is dependent from claim 6 with the additional limitation of specifying a plurality of full ray groups. Table 4 of page 11 of Gennings et al. (1998) lists a plurality of full-ray groups.

Claim 8 is dependent from claim 6 with the additional limitation of carrying out the second and third steps of instant claim 6 for the subset of agents. Gennings et al. (1997) carries out such a process in Figure 1. Specifically, in comparing the plots Figures 1a and 1b on page 200 of Gennings et al. (1997), a subset of chemicals are removed and a subset of chemical remain. As is stated in the Figure caption:

Figure 1. Three-dimensional representation of a threshold additivity surface between four chemicals over dose ranges of Chemical 1 and Chemical 2 when: (a) Chemical 3 and Chemical 4 are not included in the mixture (= 0) and (b) Chemical 3 = 0.1 and Chemical 4 = 0.1.

Consequently, while in Figure 1B, all of the constituents are in the mixture, in Figure 1A of Gennings et al. (1997), the subset of chemicals 3 and 4 are removed, leaving chemicals 1 and 2.

Claim 9 is dependent from claim 6 with the additional limitation of single chemical data being linked to a linear term in said polynomial model. The linear term in the equation on page 1 of Gennings et al. (1998) is related to single chemical data.

Claim 10 is dependent from claim 9 wherein the additivity model and mixture models are depicted as curves. Claim 13 is dependent from claim 6 with the additional limitation of generating a graphical representation of said polynomial in total dose. Figure 2 of Gennings (1998) on page 10 illustrates a comparison of additivity (i.e. model predicted) and mixture model (i.e. observed) with the purpose of comparing the two types of statistical analyses.

Claim 11 is dependent from claim 6 wherein the polynomial is embedded in a generalized linear model. Claim 12 is dependent from claim 6 wherein the polynomial is embedded in a generalized nonlinear model. The equation on page 1 of Gennings et al. (1998) illustrates both the linear and nonlinear polynomials, based on the number of

components in the mixture. While a single-component mixture exhibits linear additivity, multi-component mixtures are fit by a nonlinear model.

Claim 16 is dependent from claim 15 with the further limitation of being applicable to a plurality of full-ray groups. Table 4 of page 11 of Gennings et al. (1998) lists a plurality of full-ray groups.

Claim 18 is dependent from claim 14 by carrying Gennings et al. (1997) out such a process of eliminating a subset of agents. Specifically, in comparing the plots Figures 1a and 1b on page 200 of Gennings et al. (1997), a subset of chemicals are removed and a subset of chemical remain. As is stated in the Figure caption:

> Figure 1. Three-dimensional representation of a threshold additivity surface between four chemicals over dose ranges of Chemical 1 and Chemical 2 when: (a) Chemical 3 and Chemical 4 are not included in the mixture (= 0) and (b) Chemical 3 = 0.1 and Chemical 4 = 0.1.

Consequently, while in Figure 1B, all of the constituents are in the mixture, in Figure 1A of Gennings et al. (1997), the subset of chemicals 3 and 4 are removed, leaving chemicals 1 and 2.

Claim 20 is dependent from claim 19 with the further limitation of being applicable to a plurality of full-ray groups. Table 4 of page 11 of Gennings et al. (1998) lists a plurality of full-ray groups.

Claim 22 is dependent from claim 19 by carrying Gennings et al. (1997) out such a process of eliminating a subset of agents. Specifically, in comparing the plots Figures 1a and 1b on page 200 of Gennings et al. (1997), a subset of chemicals are removed and a subset of chemical remain. As is stated in the Figure caption:

> Figure 1. Three-dimensional representation of a threshold additivity surface between four chemicals over dose ranges of Chemical 1 and Chemical 2 when: (a) Chemical 3 and Chemical 4 are not included in the mixture (= 0) and (b) Chemical 3 = 0.1 and Chemical 4 = 0.1.

Consequently, while in Figure 1B, all of the constituents are in the mixture, in Figure 1A of Gennings et al. (1997), the subset of chemicals 3 and 4 are removed, leaving chemicals 1 and 2.

Claim 23 is dependent from claim 14 and recites a method of detecting interactions among agents in a group or mixture comprising two steps of fitting a polynomial interaction threshold model and statistically testing different parameters in the polynomial.

The study of Gennings et al. (1998), entitled, "Combination threshold models with design optimization along fixed-ratio rays," states in the abstract:

> Threshold models are useful in concentration-effect studies to describe regions of exposure that result in background response. These models are parameterized to estimate the background response, the concentration-effect relationship, and the join-point between the two, called the threshold. If the threshold is different than zero, then it can be inferred that exposure to the chemical at regions below the threshold do not increase risk above background. When the exposure is to many chemicals, fixed-ratio ray designs can be used to assess risk to single chemicals and to specified mixtures of chemicals. This article describes the inference resulting from use of a threshold model for correlated binary data supported by a ray design. An example of the effect of three hepatotoxins in the development of rats is provided. In addition, a two-stage simultaneous optimal design criterion is described for the threshold model along rays of fixed ratios. The approach is illustrated through a simulation study of the hepatotoxin data.

Consequently, Gennings et al. (1998) teaches usage of mixtures and analysis (using fixed ratio rays) of mixture data in rats (test subjects).

The first step of instant claim 23 recites fitting a polynomial additivity to dose-response data. Gennings et al. (1998) teaches the use of an additivity model in section 2.2 on page 4, entitled, "Estimation of an additivity threshold surface." The first equation in section 2.2 of Gennings et al. (1998) teaches such an additivity model quantitatively. Furthermore, the equation on page 1 of Gennings et al. (1998) illustrates such a polynomial to be used to determine additivity in dose response data. As there are three agents interacting in this specific case of Gennings et al. (1998), the highest order term that is not zero is a cubic term, indicating three components (i.e. second step of instant claim 6).

Claim 24 is dependent from claim 23 with the further limitation of being applicable to a plurality of full-ray groups. Table 4 of page 11 of Gennings et al. (1998) lists a plurality of full-ray groups.

Claim 25 is dependent from claim 23, further comprising additional steps of removing selected subsets and re-determining additivity.

The first and second steps of instant claim 25 recite removing a subset of agents from the group or mixture and repeating this step for multiple subsets, respectively. The third step of instant claim 1 recites determining the interaction of agents by utilizing the statistical methods based on the results of the third and fourth steps of the method. In

the example study in section 4 of Gennings et al. (1998) on pages 8-12 of Gennings et al. (1998), Table 4 of Gennings et al. (1998) on page 11 illustrates modeling the interaction of three agents (DEHP, HEPT, and TCE) by removing two of the three agents, and then examining the effects of a mixture on the mixture in Ray 4, which is a 70:1:29 mixture of DEHP, HEPT, and TCE, respectively. Table 3-5 on page 11-12 of Gennings et al. (1998) tabulate a plurality of full-ray groups. Figure 2 on page 10 if Gennings et al. (1998) is interpreted as a comparison between an additivity model and a mixture model.

However, Gennings et al. (1998) fails to teach that when the subsets of two agents are removed, the remaining agents (plural) must maintain their relative ratios (i.e. third step of instant claim 6).

Gennings et al. (1997) teaches such a phenomenon in their study, entitled "Detection of departures from additivity in mixtures of many chemicals with a threshold model." Specifically, in comparing the plots Figures 1a and 1b on page 200 of Gennings et al. (1997), a subset of chemicals are removed and a subset of chemical remain. As is stated in the Figure caption:

> Figure 1. Three-dimensional representation of a threshold additivity surface between four chemicals over dose ranges of Chemical 1 and Chemical 2 when: (a) Chemical 3 and Chemical 4 are not included in the mixture (= 0) and (b) Chemical 3 = 0.1 and Chemical 4 = 0.1.

Consequently, while in Figure 1B, all of the constituents are in the mixture, in Figure 1A of Gennings et al. (1997), the subset of chemicals 3 and 4 are removed, leaving chemicals 1 and 2.

Claim 26 is dependent from claim 23 with the additional limitation of having single chemical data wherein the single chemical data is obtained in test subjects.

The study of Gennings et al. (1998), entitled, "Combination threshold models with design optimization along fixed-ratio rays," states in the abstract:

> Threshold models are useful in concentration-effect studies to describe regions of exposure that result in background response. These models are parameterized to estimate the background response, the concentration-effect relationship, and the join-point between the two, called the threshold. If the threshold is different than zero, then it can be inferred that exposure to the chemical at regions below the threshold do not increase risk above background. When the exposure is to many chemicals, fixed-ratio ray designs can be used to assess risk to single chemicals and to specified mixtures of chemicals. This article describes the inference resulting from use of a threshold model for correlated binary data supported by a ray design. An example of the effect of three hepatotoxins in the development of rats is provided. In addition, a two-stage simultaneous optimal design criterion is described for the threshold model along rays of fixed ratios. The approach is illustrated through a simulation study of the hepatotoxin data.

Consequently, Gennings et al. (1998) teaches usage of mixtures and analysis (using fixed ratio rays) of mixture data in rats (test subjects).

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the fixed ratio ray optimization study of Gennings et al. (1998) by use of the additivity models of Gennings et al. (1997) wherein the motivation would have been that while Gennings et al. (1998) measures fixed ratio rays in simple ternary systems, Gennings et al. (1997) uses analogous principles with the advantage of investigating additivity in more complex quaternary mixtures [see introduction of Gennings et al. (1997)].

Response to Arguments:

Applicant's arguments filed 27 November 2007 have been fully considered but they are not persuasive.

Applicant first argues on page 16 of the Remarks that the remaining steps of claim 1 teaching statistical analysis are not supplied by any of the Gennings et al. references. This is not found to be persuasive because Figure 2 of Gennings et al. (1998) teaches a statistical comparison between additivity and mixture models.

Applicant continues to argue on page 16 of the Remarks that Figure 1 of Gennings et al. (1997) is a hypothetical concept. For the reasoning discussed above, Figure 1 of Gennings et al. (1997) is interpreted to be actual data (wherein the plot can to be reconstructed using the data and relations in Gennings et al. (1997)).

Applicant next argues on page 17 of the Remarks that repetition of removal of agents in a group is not taught in Gennings et al. (1997). However, Gennings et al. (1998) teaches such a repetition (i.e. see Tables 3 and 4 on page 11).

Applicant reiterates that Gennings et al. is not an anticipatory reference for claim 14 and therefore should not be valid as an obviousness reference for any reference depending from claim 14. For the reasoning discussed above, the examiner maintains that Gennings et al. (1997) anticipates claim 14 and is therefore properly applied in the rejection above.

The declaration under 37 CFR 1.132 filed 30 November 2007 is insufficient to overcome the rejection of claims 1-13, 15-26 and 30-31 based upon 35 U.S.C. 103 as set forth in the last Office action because:

Applicant submits a declaration by Richard Allan Carchman which is an opinion declaration expressing long felt need of the application. When reviewing expert opinion (in this case for long felt need), four factors must be considered: a) the nature of the

matter sought to be established; b) the opposing evidence; c) if the expert has a vested interest in the application; and d) the validity or factual basis of the opinion.

a) The nature of the matter sought to be established is the overcoming of a 35 U.S.C. 103 rejection involving the combination of Gennings et al. (1997) and Gennings et al. (1998) by asserting an opinion declaration supporting a long felt need for the combination.

b) The opposing evidence is a strong 35 U.S.C. 103 rejection involving two related articles by Gennings et al. on threshold models; the motivation to combine is set forth above. Applicant is reminded that long felt need is a secondary consideration that must be weighed against the prima facie case of obviousness, the primary consideration. MPEP section 716.01(d) emphasizes that secondary considerations (i.e. long felt need) are secondary and do not necessarily overcome strong 35 U.S.C. 103 Rejections.

c) It is assumed that the declarant has no vested interest in outcome of this invention.

d) The declaration is in the form of an opinion declaration supported by factual evidence to support the opinion. The declarant argues that upon reading Teuschler et al., that at the time of publication, one skilled in the art would have recognized that there was a long felt need for practical methods to predict drug/agent interactions in the absence of obtaining “exhaustive factorial" data. The declarant also argues that upon reading Monosson, that at the time of publication, one skilled in the art would have recognized that there was a long felt need for practical methods to predict drug/agent

interactions. However, MPEP section 716.01(b) states that there must be a specific nexus between such evidence and the recitations of the set of claims. While Teuschler et al. explains that there is a need for advanced statistical modeling of mixtures and Monosson explains that there is a need for mixture modeling and drug/agent interaction, the evidence does not provide a nexus between the more general statistical and mixture models and the specifically claimed invention. In other words, while the evidence expresses a need for more general mixture modeling, there is no indication in the references that there is a specific need for the method of the instant application, and how the instant application overcomes this long felt need.

Consequently, the declaration is not persuasive and does not overcome the 35 U.S.C. 103 Rejection.

The Following rejection is newly applied:

Claims 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gennings et al. (1997) in view of Gennings et al. (1998) as applied to claims 1-26 above, and further in view of Rosenberg [US PGPUB 2003/0023951 published 30 January 2003; filed 5 April 2001].

Claims 30 and 31 are directed to software for carrying out the method steps of claims 1 and 6, respectively.

Gennings et al. (1997) and Gennings et al. (1998) make obvious the method for measuring additivity in mixtures as described in claims 1 and 6, as discussed above.

Gennings et al. (1997) and Gennings et al. (1998) do not teach the software required to execute the statistical methods.

The application of Rosenberg teaches MATLAB for advanced statistical modeling and data analysis (see title and abstract). MATLAB is computer software that automates mathematical calculations.

It would have been obvious to someone or ordinary skill in the art at the time of the instant invention to automate the mixture methods of Gennings et al (1997) and Gennings et al. (1998) by use of the automated statistical techniques of Rosenberg wherein the motivation would have been that the statistical analysis of MATLAB in Rosenberg enables automated and more efficient calculation of statistical data [see title, and abstract of Rosenberg].

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/RSN/
19 February 2008

/Marjorie A. Moran/
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2/19/08